

Association of blood pressure with clinical outcomes in older adults with chronic kidney disease

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Abstract

Background: in chronic kidney disease (CKD), hypertension is associated with poor outcomes at ages <70 years. At older ages, this association is unclear. We tested 10-year mortality and cardiovascular outcomes by clinical systolic blood pressure (SBP) in older CKD Stages 3 and 4 patients without diabetes or proteinuria.

Methods: retrospective cohort in population representative primary care electronic medical records linked to hospital data from the UK. CKD staged by CKD-EPI equation (≥ 2 creatinine measurements ≥ 90 days apart). SBPs were 3-year medians before baseline, with mean follow-up 5.7 years. Cox competing models accounted for mortality.

Results: about 158,713 subjects with CKD3 and 6,611 with CKD4 met inclusion criteria. Mortality increased with increasing CKD stage in all subjects aged >60. In the 70 plus group with SBPs 140–169 mmHg, there was no increase in mortality, versus SBP 130–139. Similarly, SBPs 140–169 mmHg were not associated with increased incident heart failure, stroke or myocardial infarctions. SBPs <120 mmHg were associated with increased mortality and cardiovascular risk. At ages 60–69, there was increased mortality at SBP <120 and SBP >150 mmHg.

Results were little altered after excluding those with declining SBPs during 5 years before baseline, or for longer-term outcomes (5–10 years after baseline).

Conclusions: in older primary care patients, CKD3 or 4 was the dominant outcome predictor. SBP 140–169 mmHg having little additional predictive value, <120 mmHg was associated with increased mortality. Prospective studies of representative older adults with CKD are required to establish optimum BP targets.

Keywords

blood pressure, chronic kidney disease, older people, cardiovascular outcomes

Key points

- This study examined a large sample of 158,713 older adults with chronic kidney disease (CKD) 3 or 4, free of diabetes or proteinuria.
- Systolic BPs substantially higher than current targets did not increase mortality or incident cardiovascular outcomes.
- Systolic BPs <120 and 120–129 mmHg were associated with excess mortality.
- Results suggest renal stage is a better predictor of clinical outcomes than BP in older adults.
- Research is required to establish evidence-based BP targets specific to older patients with Stages 3 and 4 CKD.

Introduction

Chronic kidney disease (CKD) is common in older adults and is an established risk factor for mortality and cardiovascular events [1]. Kidney disease: improving global outcomes (KDIGO) described the grading system used internationally for CKD, with Grade 3 representing moderate impairment, Grade 4 severe impairment and Grade 5 kidney failure [2]. Global estimates of CKD3–5 prevalence for adults over 70 years range from 14.1% in the Netherlands to 56.6% in Ireland, higher in women [3, 4]. CKD and hypertension frequently co-exist and independently increase the risk of cardiovascular outcomes [1, 5, 6]. Blood pressure (BP) management is a key aspect of CKD clinical care. However, studies incorporated into guidelines on BP in CKD largely exclude adults older than 70 years [7], despite comprising over half of the CKD population [8].

Debate continues about safe levels of BP reduction in older adults. Until recently, the consensus internationally for older adults with CKD without diabetes or significant proteinuria was to control BP to a target of <140/90 mmHg [7, 9, 10]. CKD guidelines do not specifically recommend adjustments for BP management in older adults. The recently published American College of Cardiology/American Heart Association hypertension guidelines [11] suggest a ‘team-based approach to risk/benefit’ in older adults, but currently BP-associated prognosis in older adults with moderate to severe CKD is not known [6].

Weiss *et al.* [12] investigated Systolic BP (SBP) and mortality in older adults with CKD and found that the relationship varied with age: a U-shaped mortality curve at age 65–70, but no increased mortality in adults aged over 70 years at SBP >140 mmHg, compared to 131–140 mmHg, and higher mortality at SBP <130 mmHg. However, the study did not report cardiovascular outcomes or allow for BP dynamics. We have recently shown BPs decline from 14 to 18 years prior to death [13], potentially biasing observational studies by confusing cause and effect.

The Systolic Blood Pressure Intervention Trial (SPRINT) [14] enrolled adults with high cardiovascular risks taking antihypertensive medication with SBP between 130 and 139 mmHg, and studied the effect of reducing SBP to a target of <120 mmHg. In a predefined CKD sub-analysis (mean age 71.9 with 43.9% aged ≥75), the composite cardiovascular trended lower in the intervention group, but did not reach significance (hazard ratio (HR) 0.81; 95% CI, 0.63–1.05), and intervention group overall mortality outcome was lower (HR, 0.72; 95% CI, 0.53–0.99). Importantly, there was no evidence of effect modification comparing those with and without CKD. Although the SPRINT trial clearly provides more robust evidence than observational studies, it does have limitations: e.g. those with cognitive impairment, unable to stand or in a nursing home were excluded; CKD in SPRINT was relatively mild Grade 3 CKD with a mean estimated Glomerular Filtration Rate (eGFR) of 47.4 ml/min per 1.73 m²; 11% withdrew consent or were lost to follow-up, and separate results for the 75 plus group were not reported. Also, the trial was

stopped after a 3.3 years median follow-up due to evidence of overall benefit across the intervention group, with ascertainment of longer-term outcomes therefore necessarily remaining unmeasured.

In this observational analysis, we aimed to estimate mortality and cardiovascular outcomes in a representative, population-based cohort aged over 60 years (for comparison with existing studies), with CKD3 and 4, according to SBP, followed for up to 10 years. We used large-scale data from the Clinical Practice Research Datalink (CPRD) of primary care medical records. CPRD includes routine clinical measurements of creatinine and BP linked to clinical records. CKD3 and 4 were the focus population of this study to encompass older adults with clinically significant renal impairment but predominantly cared for in primary care.

Methods

Data source

We used data from the Clinical Practice Research Datalink (CPRD), which provides anonymised primary care data for over 11.3 million patients from 674 UK community practices for health research [8]. The CPRD is linked to hospital episode statistics (HES) and death certification. Ethical approval was granted by the Independent Scientific Advisory Committee for UK Medicines and Healthcare Products Regulatory Agency database research (ISAC) under protocol number 14_135 and 14_135RA. The CPRD is shown to be representative of the UK population for age, sex and ethnicity [15], and to have good external validity for CKD [16] and cardiovascular disease [17]. The CPRD obtained Multiple Research Ethics Committee approval (05/MRE04/87) to undertake purely observational studies. CPRD is also covered by NIGB-ECC approval ECC 5–05 (a) 2012.

Sample selection

Adults aged over 60 years were included, with age categories 60–70 years, for comparison with previous studies, and over 70 years. The index date was the date when all selection criteria were met, between 1 January 2000 and 14 November 2014.

We focussed on CKD3 and 4, excluding CKD 5 (eGFR <15 ml/min/1.73 m²) who have a different risk profile [8, 18], and are largely managed in secondary care. We excluded previous renal transplant and polycystic kidney disease due to mechanisms that may alter relationship with BP. We excluded pre-existing diabetes, as defined by the Quality and Outcomes Framework business rules at index date [19] which are used to identify adults within primary care with clinically diagnosed diabetes. We also excluded significant proteinuria (>30 mg/mmol Albumin Creatinine Ratio or equivalent in recorded laboratory values or medical read codes for proteinuria), as these groups have different risk profiles and are subject to different clinical guidelines.

In order to minimise reverse causation, we excluded prevalent heart failure, dementia, cancer and those within 6 months of death, who would have increased mortality and potentially declining BP trends.

CKD and blood pressure measures

The eGFR was calculated from creatinine, based on the CKD-Epidemiology Collaboration (CKD-EPI) equation [20], shown to be valid in older adults [21]. The CKD category was derived from eGFR according to KDIGO definitions [2]. Two eGFR measurements in the same CKD category were required over 90 days apart, as per clinical guidelines [7], within 3 years prior to index date.

BP values were from routine clinical measurements. To minimise potential bias due to atypical values obtained during acute illness, we used median BP from the 3 years prior to index date. The main analysis focuses on those without declining BP in the 5 years prior to index date, as we previously described declining BP trajectories over 10 years prior to death [13].

Outcomes

Follow-up was for a maximum of 10 years, until death or study end date of 14 November 2014.

The outcomes of interest were all-cause mortality and incident cardiovascular disease: ischaemic stroke (stroke), myocardial infarction or cardiac revascularisation procedure (MIP) and heart failure. All-cause mortality was established from HES codes and office of national statistics (ONS).

Incident cases of stroke, MIP, and heart failure were established from HES and primary care Read Codes specific to the conditions. We used HES for stroke outcomes to increase specificity for ischaemic stroke [22]. In addition, for MIP we used the Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4 (OPCS) [23] to increase yield of clinically significant coronary artery disease by including coronary angioplasty and coronary artery bypass graft procedures.

Covariates

Sex, age, year of index date (for clinical practice changes), social deprivation status, smoking status, BMI category and alcohol status were adjusted for in the main study models (see Appendix 1, available at *Age and Ageing* online). These covariates were adjusted for in mortality and cardiovascular analyses.

Sensitivity analyses

We investigated the effect of diastolic BP on outcomes separately, with the same adjustments and methods as for SBP. We conducted overall subgroup analyses by sex and for those with declining BPs. To address possible reverse causation, for example from clinically undiagnosed heart failure, we performed a sensitivity analysis censoring the first 5

years of follow-up, which also provided information about longer-term outcomes given that existing studies have been largely restricted to <4 years [7, 24]. In addition, we performed a sensitivity analysis stratifying by Charlson comorbidity index to check whether results were different according to comorbid status [25].

Statistical analysis

Statistical analysis was performed using Stata v14.1.

We used Cox proportional hazards models to estimate associations between CKD grade, baseline SBP and all-cause mortality and Fine and Gray competing risk models [26] for cardiovascular outcomes, with all-cause mortality as the competing risk.

Analyses were stratified according to age group (60–70 and 70+) and CKD stage (3 or 4). The comparison group was attained SBP 130–139 mmHg, in keeping with current international guidelines [7, 10, 27].

Missing data

Clinical information within the study was felt likely to be missing not at random. Cohort selection was determined by laboratory identification of CKD and BPs collected by routine clinical measurements. Therefore, those with less healthcare seeking behaviour may be under-represented in this study. However, in the UK over 98% of the population are registered with a primary healthcare provider and consultations are free of charge [28].

Loss to follow-up in this routinely collected dataset is possible for those who transfer out of the CPRD participating practices prior to the end of follow-up or death, but mortality outcomes were obtained from national health certification and so are near complete. Loss to follow-up other than mortality can occur on change of practice and therefore is likely to be a combination of those who move into a formal care setting outside their previous area and those who are healthy and relocate. Those transferred out of the practice were censored.

Results

About 165,324 subjects met inclusion criteria for this analysis, 158,713 (96%) with CKD3 and 6,611 with CKD4. The mean age was 76 years (range 60–107), and 63% were women. Baseline characteristics and incident outcomes are summarised in Table 1. Maximum follow-up was 10 years (mean = 5.7 years, SD 3.12). During the follow-up period 50,715 (30.7%) participants died, 8,753 (5.2%) had incident MIP, 13,864 (8.4%) stroke and 10,602 (6.4%) heart failure.

Survival by CKD stage

Mortality was substantially higher for CKD4 compared with CKD3 (see Appendix 2, available at *Age and Ageing* online), in both age-groups. All studied cardiovascular

Table 1. Characteristics of the sample by CKD grade at baseline

	CKD3	CKD4
Overall		
N (%)	158,713 (96)	6,611 (4)
Age in years, mean (SD)	76.5 (8.4)	82.0 (9.2)
Female (%)	100,518 (63)	4,112 (62)
Median SBP mmHg (SD)	145 (15.4)	146 (17.4)
Median DBP mmHg (SD)	80 (7.9)	80 (8.6)
Mean GFR ml/min per 1.73 m ² (SD)	48.8 (7.5)	23.9 (4.0)
Incident MI, N (%)	8,317 (5)	436 (7)
Incident IS, N (%)	13,265 (8)	599 (9)
Incident HF, N (%)	9,961 (6)	641 (10)
Died, N (%)	46,886 (29)	3,829 (58)
Over 70 years		
N (%)	66,974 (97)	1,940 (3)
Female (%)	41,162 (61)	1,151 (59)
Median SBP mmHg (SD)	145 (15.2)	148 (17.3)
Median DBP mmHg (SD)	80 (7.7)	76 (4.4)
Mean GFR ml/min per 1.73 m ² (SD)	48.0 (7.5)	24.1 (3.9)
Incident MI, N (%)	3,828 (6)	139 (7)
Incident IS, N (%)	5,950 (9)	191 (10)
Incident HF, N (%)	4,376 (7)	213 (10)
Death, N (%)	17,709 (26)	3,798 (55)

outcomes were increased in CKD4 compared to CKD3 (see Appendix 3, available at *Age and Ageing* online).

Mortality outcomes by SBP

With baseline CKD3 (see Figure 1), HRs of mortality were U-shaped in adults aged 60–70, with increased mortality at SBP >150 mmHg compared with SBP 130–139 mmHg. However, for over 70 years with CKD3 the mortality HR did not increase until SBP ≥180 mmHg. All with CKD3 at baseline had increased mortality with SBP <120 mmHg and 120–129 mmHg. With CKD4 at baseline, those aged over 70 again had no significant increase in mortality risk with SBPs over the current target from 140–170 mmHg.

Cardiovascular outcomes by SBP

In adults over 70 with CKD3 or 4, the stroke HR did not increase (Table 2), even with SBPs of 140–180 mmHg; significantly higher than recommended target, while for 60–70 year olds there was a trend to increased hazards at increased SBP. SBPs up to 160 mmHg were not associated with statistically significant increased risk of incident MIP in adults over 70 with either CKD3 or 4 at baseline.

The HR for incident heart failure was raised in SBP categories <120 and 120–129 mmHg in adults over 70 with CKD3 or 4, but there was no increased risk at SBPs over the target BP of 130–139 mmHg and up to 180 mmHg.

Sensitivity analyses

Sensitivity analyses are presented in Appendices 5–12, available at *Age and Ageing* online.

Diastolic BP (DBP) of <70 mmHg was associated with increased mortality in adults 60–70 years and over 70 with CKD3 and 60–70 with CKD4 (see Appendix 5, available at *Age and Ageing* online). There was no significant difference in mortality HR between the 80–89 and 90–99 mmHg in adults 60–70 years and over 70 with CKD3 or 4. Cardiovascular outcomes with DBP varied with outcome, CKD and age group (see Appendix 6, available at *Age and Ageing* online).

Mortality outcomes were similar for men and women (see Appendix 7, available at *Age and Ageing* online). Elevated SBP had a higher HR for stroke outcomes in men than women (see Appendix 8, available at *Age and Ageing* online) with both CKD3 and 4, while results for MIP and heart failure were similar for men and women.

Analysis of longer-term outcomes (5–10 years) produced similar results to the main analysis (see Appendices 9 and 10, available at *Age and Ageing* online), as did declining BP trajectories (see Appendices 11 and 12, available at *Age and Ageing* online).

Consistent results were produced across categories of Charlson comorbidity index (0, 1–2, 3–4 and ≥5) (see Appendix 13, available at *Age and Ageing* online).

Discussion

Previous studies have provided clear evidence that both CKD stage [29] and BP lowering [24, 30] are predictive of outcomes in adults aged up to 70 years old, but evidence at older ages was less clear. In this large-scale study of older primary care patients with CKD3 and 4 (but free of diabetes or proteinuria), we found that in subjects aged 70+, routine clinical SBPs 140–169 mmHg were not associated with excess mortality or incident cardiovascular morbidity, compared to achieving SBPs of 130–140 mmHg. Conversely, SBPs of <120 mmHg were associated with worse prognosis.

Our findings are consistent with El Nahas *et al.* [6], who argued the high prevalence of CKD in older adults represents accumulation of cardiovascular disease and atherosclerosis, diffuse ‘cardio-kidney damage’. This cumulative end-organ damage appears more influential on cardiovascular and mortality outcomes than the current BP.

The changing relationship between SBP and mortality in older adults with CKD was previously described by Weiss *et al.* [12], who reported analysis of SBP and all-cause mortality in 21,015 adults over 65 from Northwest United States, with 3.53 years median follow-up. Our mortality results are consistent with this analysis, which found that all-cause mortality was elevated with SBP >140 mmHg for adults 65–70, but in adults over 70 all-cause mortality was no different with SBP >140 mmHg compared to the reference group. Our study is a major extension of this work. Weiss *et al.* [12] did not evaluate cardiovascular outcomes and included some conditions at baseline that may cause reverse causation, such as diabetes. However, they report a sensitivity analysis excluding heart failure produced similar results.

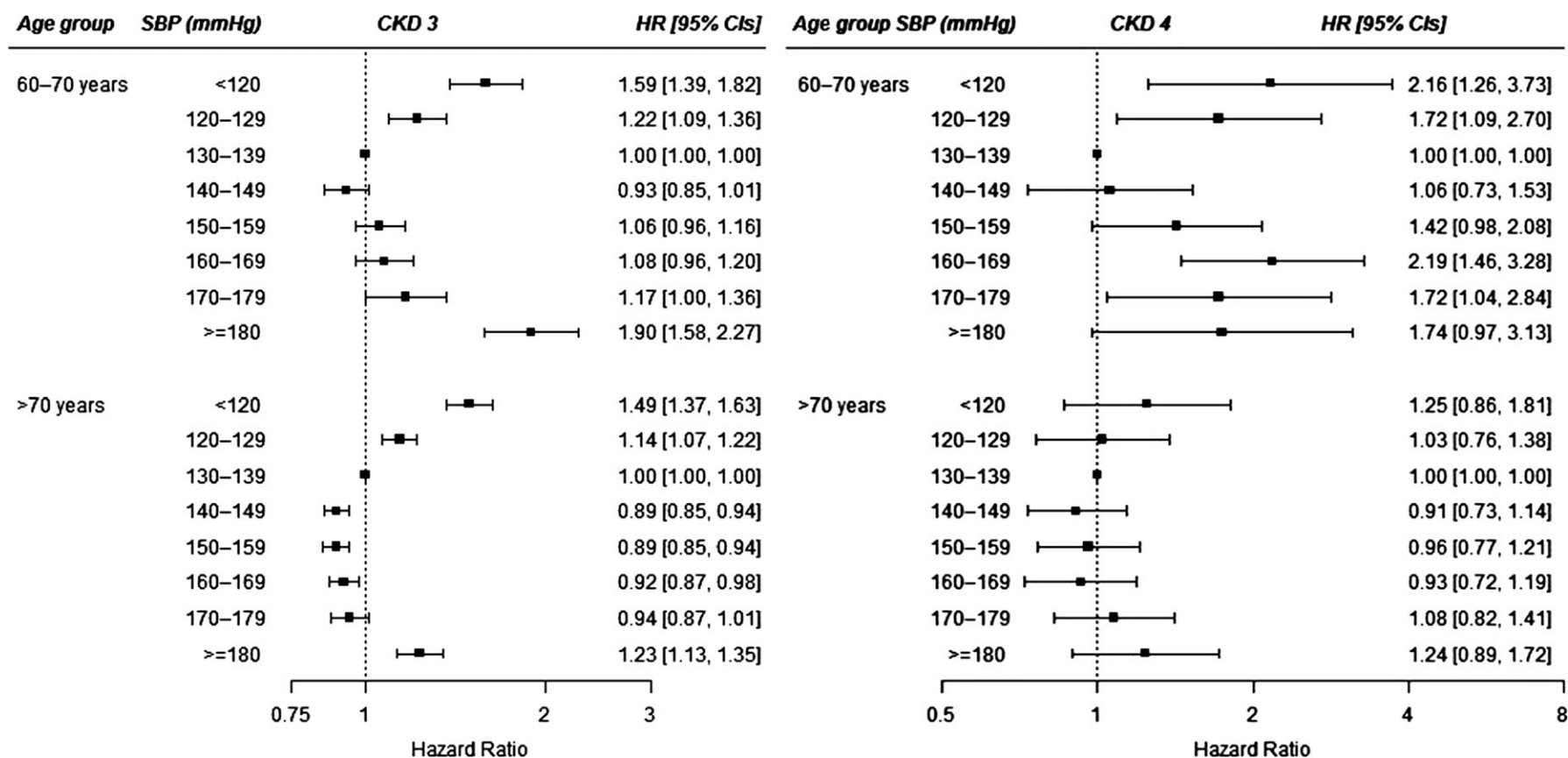


Figure 1. Adjusted associations (Hazard ratios) of systolic blood pressure and mortality in older adults with CKD3 and CKD4, stratified by age group.

Table 2. Associations (Hazard ratios) of systolic blood pressure and cardiovascular outcomes in older adults with CKD3 and 4, stratified by age group

Systolic blood pressure (mmHg)	Age 60–70 years			Age > 70 years		
	Myocardial infarction HR (95% Confidence interval)	Heart failure HR (95% CI)	Stroke HR (95% CI)	Myocardial infarction or procedure HR (95% CI)	Heart failure HR (95% CI)	Stroke HR (95% CI)
Chronic kidney disease 3 at baseline						
<120	0.86 (0.64–1.16)	1.90 (1.50–2.40)**	0.98 (0.76–1.27)	1.38 (1.13–1.68)**	1.66 (1.40–1.96)**	0.96 (0.80–1.15)
120–129	0.96 (0.78–1.17)	1.21 (0.99–1.48)	0.99 (0.82–1.19)	1.04 (0.89–1.21)	1.21 (1.07–1.38)**	0.93 (0.82–1.05)
130–139 (reference category)	1	1	1	1	1	1
140–149	0.84 (0.72–0.98)*	0.91 (0.78–1.07)	0.97 (0.85–1.11)	0.99 (0.89–1.10)	0.90 (0.82–0.99)*	0.99 (0.91–1.07)
150–159	1.04 (0.88–1.22)	0.80 (0.66–0.95)*	1.11 (0.96–1.28)	0.97 (0.87–1.09)	0.83 (0.75–0.92)**	0.95 (0.87–1.03)
160–169	1.03 (0.85–1.24)	0.98 (0.81–1.20)	1.19 (1.00–1.40)*	1.12 (0.99–1.26)	0.86 (0.77–0.97)*	0.97 (0.88–1.06)
170–179	0.91 (0.68–1.22)	1.04 (0.79–1.38)	1.23 (0.97–1.56)	1.06 (0.90–1.23)	0.96 (0.83–1.11)	1.00 (0.88–1.13)
≥180	1.13 (0.77–1.67)	1.26 (0.87–1.82)	1.74 (1.30–2.32)**	1.40 (1.16–1.69)**	1.18 (0.99–1.40)	1.28 (1.10–1.49)**
Chronic kidney disease 4 at baseline						
<120	Insufficient data	2.08 (0.76–5.71)	2.76 (0.82–9.27)	1.27 (0.41–3.89)	1.78 (0.77–4.12)	1.09 (0.45–2.66)
120–129	1.37 (0.45–4.14)	0.38 (0.09–1.68)	1.40 (0.47–4.2)	1.11 (0.47–2.67)	1.83 (0.95–3.51)	1.08 (0.57–2.05)
130–139 (reference category)	1	1	1	1	1	1
140–149	1.34 (0.59–3.04)	0.68 (0.32–1.45)	1.48 (0.68–3.22)	0.98 (0.51–1.86)	1.10 (0.64–1.90)	0.73 (0.43–1.24)
150–159	1.96 (0.86–4.48)	1.18 (0.57–2.45)	2.16 (1.00–4.68)	0.83 (0.42–1.63)	1.27 (0.73–2.19)	0.86 (0.51–1.45)
160–169	1.64 (0.57–4.69)	1.22 (0.52–2.86)	2.01 (0.82–4.93)	1.21 (0.61–2.39)	1.13 (0.62–2.05)	1.03 (0.59–1.79)
170–179	0.39 (0.05–3.23)	1.48 (0.58–3.80)	0.72 (0.15–3.49)	1.63 (0.80–3.33)	1.69 (0.93–3.08)	0.84 (0.44–1.60)
≥180	3.68 (1.45–9.35)	0.70 (0.16–3.08)	2.46 (0.82–7.34)	1.61 (0.67–3.84)	1.05 (0.45–2.45)	1.05 (0.48–2.27)

P* value <0.05; *P* value <0.01.

We described the SPRINT randomised trial [14] CKD sub-study in our introduction. Randomised trials provide robust evidence on treatment effects and cannot be directly compared to our observational results which focus on prognosis. The SPRINT CKD recruited patient group differed from the group we studied: for example, the all-cause death rate in the SPRINT CKD sub-study control group (mean age 71) was 2.21% per year, but in our sample (mean age 76) the death rate was 5.38% per year (95%CI 5.34%–5.42%, $n = 50,715/165,324$ over 5.7 year mean follow-up, 5.2% in CKD3, 10.2% in CKD4). The results of SPRINT are clearly more robust than observational studies, but questions do remain for the routine long-term care of the full range of typical older groups managed in primary care, who often continue with antihypertensive medications for many years. As our subjects represent whole older populations (virtually all older people are registered with primary care, including those with cognitive impairments and in institutional settings) with practically complete follow-up through the national hospital and death certification systems, our estimates of prognosis may be informative for developing treatment approaches for the wider older population.

A systematic review and meta-analysis by Malhotra *et al.* [24] investigated mortality outcomes in adults with CKD3–5 according to intensity of BP control. Included trials decreased mean SBP to 132 mmHg in the intensive arm and to 140 mmHg in the less intensive arms, with median follow-up of 3.6 years and a mean difference in SBP of 10 mmHg between the two groups. The overall odds ratio for all-cause mortality was reported as 0.86 (95% CI, 0.76–0.97; $P = 0.01$) for more intensive versus less

intensive BP control. While some of the included studies were focussed on older adults (e.g. the Hypertension in the Very Elderly Trial (HYVET) [31]), outcomes for older adults were not reported separately.

Our study has a number of key strengths. We report the results of the largest cohort study on BP that has been conducted in older adults with established CKD. A particular strength of our analysis is the representative nature of the cohort for older adults in the general population. We have included a substantial median follow-up (5.7 years, maximum 10). We have accounted for BP dynamics and shown that results are similar with stable or declining BPs, as well as for long-term and short-term follow-up.

There are inevitably limitations of our analyses. This is prospective observational analysis using existing data—the exposure status was collected prior to the outcome data, however it was not a controlled trial and could therefore be subject to unmeasured confounding. We have adjusted for relevant measured potential confounding factors and additionally conducted sensitivity analyses. Data on proteinuria were only available for a limited proportion of those with CKD3 and 4, but those with significant proteinuria or diabetes were excluded as these groups are subject to different clinical guidelines and should be considered separately.

An important difference with trials such as SPRINT is that our BP measurements were from clinical routine data, which can provide higher BP measures than BPs taken under research conditions [32]. However, in our analyses we used median BP recorded over 3-year periods prior to index date. In addition to giving stable overall estimates, 3-year mean BPs should have removed the effects of atypical

values for each patient, for example those obtained during acute illness. Finally, the BP measures were those that family physicians were using to guide clinical decisions, and therefore have validity in estimating prognosis in typical care settings. Our results that, e.g. we observed no increase mortality in the 70 plus group with SBPs from 160 to 169 mmHg (versus SBP 130–139) appears difficult to explain away with the usually modestly lower SBPs in both the high SBP group and the comparison category that might have been measured in research settings.

The majority of the cohort had CKD3, leading to small sample sizes within SBP categories of CKD4 and wide confidence intervals. More work is required into prognosis by attained SBP in older adults with CKD3 and 4 and significant proteinuria or co-existing diabetes.

Although we have tried to minimise confounding, residual confounding is always possible in observational studies, and our results should be regarded as estimates of observed prognosis rather than necessarily being directly driven only by antihypertensive medication effects. The evidence presented, however, suggests the need for further work, preferably including randomised trials, to provide a stronger evidence base for current BP targets in older CKD patients without diabetes.

Conclusion

This large-scale analysis of attained SBP in a representative cohort of older adults with CKD3 and 4 provides further evidence that older adults have different prognoses from relatively younger or healthier adults. We found that SBP up to 169 mmHg were not associated with increased mortality or heart failure in adults over 70 compared with BP 130–140 mmHg, while SBP of 120–129 mmHg and <120 mmHg were associated with worse prognosis. Approaches to clinical management of SBP in older patients with CKD should not necessarily be based on extrapolating findings from younger groups. Further prospective studies, preferably including randomised trials, are required in representative older adults to establish optimum BP targets in older adults with CKD.

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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